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(71) Applicant (for all designated States except US): **SCHERING AKTIENGESSELLSCHAFT** [DE/DE]; D-13342 Berlin (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **HEIL, Wolfgang** [DE/DE]; Münchener Strasse 26/27, D-10825 Berlin (DE).
HILMAN, Jürgen [DE/DE]; Ugandastrasse 9, D-13351

Berlin (DE). **LIPP, Ralph** [DE/DE]; Holzungsweg 63, D-14169 Berlin (DE). **HEITHECKER, Renate** [DE/DE]; Wolzogenstrasse 15, D-14163 Berlin (DE).

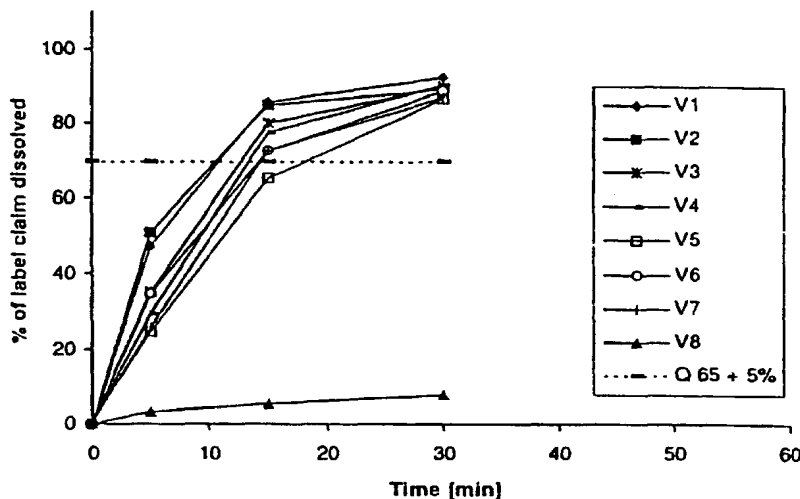
(74) Agent: **THORSEN, Jesper**; Plougmann, Vingtoft & Partners A/S, Sankt Annæ Plads 11, P.O. Box 3007, DK-1021 Copenhagen K (DK).

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(54) Title: PHARMACEUTICAL COMBINATION OF ETHINYLESTRADIOL AND DROSPIRENONE FOR USE AS A CONTRACEPTIVE



(57) Abstract: A pharmaceutical composition comprises, as a first active agent, 6 β , 7 β ; 15 β , 16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (drospirenone) in an amount corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and, as a second active agent, 17 α -ethinylestradiol (ethinylestradiol) in an amount corresponding to a daily dosage of from about 0.01 mg to about 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients. In a specific embodiment, the composition consists of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein said daily dosage units comprise the combination of drospirenone and ethinylestradiol. The composition may further comprise 7 or less daily dosage units containing no active agent or containing ethinylestradiol alone.



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PHARMACEUTICAL COMBINATION OF ETHINYLESTRADIOL AND DROSPIRENONE FOR USE AS A CONTRACEPTIVE

FIELD OF THE INVENTION

5 The present invention relates to a pharmaceutical composition comprising drospirenone and ethinylestradiol, a method of providing dissolution of drospirenone, methods of inhibiting ovulation by administration of drospirenone and the use of drospirenone and ethinylestradiol for inhibiting ovulation.

10 BACKGROUND OF THE INVENTION

Oral contraceptives containing a combination of a gestagen and an estrogen component have been used since the 1960's. The earliest contraceptive preparations consisted of 21 tablets containing the combination of active agents and 7 tablets containing no active agent, and the amount of each active agent was the same in each tablet (the so-called one-phase preparations). Subsequently, preparations were developed that consisted of tablets containing different amounts and ratios of the active agents over the cycle of administration (the so-called multiple-phase preparations).

20 Contraceptive reliability is mainly provided by the gestagen component. The daily dosage should be at least the minimum of what is needed for the gestagen in question to inhibit ovulation effectively. The estrogen component acts to increase the ovulation inhibitory effect of gestagen and to ensure cycle stability. Since the introduction of oral contraceptives, the daily dosage of gestagen has been reduced through the development of new and more efficient gestagens than were present in the earlier contraceptive preparations. It has also been possible to reduce the daily dosage of estrogen.

6 β ,7 β ;15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (drospirenone) is known from DE 26 52 761 in which its use as a diuretic compound is disclosed.

30

In DE 30 22 337, the gestagen-like activity of the compound and its consequent utility as a contraceptive agent is described at dosage levels of 0.5-50 mg of drospirenone per day. It is also noted that the mechanism of action of the compound is very similar to that of the natural corpus luteum hormone progesterone, and that it does not give rise to increased blood pressure for which reason it may be administered to women who have or are at risk

of developing increased blood pressure. It is further described that drospirenone may be administered together with ethinylestradiol in an amount of 0.03-0.05 mg per day.

DE 30 51 166 discloses the use of the drospirenone for the treatment of gynaecological irregularities and for contraception at a dosage level of 0.5-50 mg per day.

EP 398 460 discloses the use of drospirenone for the treatment of androgen-induced disorders, aldosterone-induced disorders and hormonal irregularities as well as for contraception at dosage levels of 0.5-50 mg, preferably 1-10 mg per day. Ethinylestradiol may be co-administered at a level of 0.02-0.04 mg per day.

US 5,756,490 discloses pharmaceutical combination preparations comprising 23 or 24 dosage units containing a combination of a gestagen and an estrogen and 4-10 dosage units containing estrogen alone. Drospirenone is mentioned as a possible, but not preferred, gestagenic compound and ethinylestradiol is mentioned as a possible, but not preferred, estrogenic compound.

SUMMARY OF THE INVENTION

In the course of research leading to the present invention, it has surprisingly been found that a hitherto undisclosed minimum dosage level of drospirenone is required for reliable contraceptive activity. Similarly, a preferred maximum dosage has been identified at which unpleasant side effects, in particular excessive diuresis, may substantially be avoided.

Accordingly, in a first aspect, the present invention relates to a pharmaceutical composition comprising, as a first active agent, 6 β ,7 β ;15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (drospirenone) in an amount corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and, as a second active agent, 17 α -ethinylestradiol (ethinylestradiol) in an amount corresponding to a daily dosage of from about 0.01 mg to about 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients.

Apart from the active substances themselves, it is envisaged that an ester or prodrug of drospirenone may be employed in the present composition, e.g. an oxyiminopregnane

carbolactone as disclosed in WO 98/24801. Likewise, it is envisaged that esters or ethers of ethinylestradiol may be included in the composition.

- In a further aspect, the invention relates to a method of inhibiting ovulation in a mammal, in particular a human, comprising administering, to said mammal, drospirenone in an amount in the range of from about 2 mg to about 4 mg of per day, together with ethinylestradiol in an amount of from about 0.01 mg to about 0.05 mg per day, said amounts being effective to inhibit ovulation in said mammal.
- 10 In a still further aspect, the invention relates to the use of drospirenone combined with ethinylestradiol for preparing a pharmaceutical preparation for the inhibition of ovulation in a mammal, in particular a human, the composition comprising an amount of drospirenone corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and comprising an amount of ethinylestradiol corresponding to a daily
- 15 dosage, on administration of the composition, of from about 0.01 to about 0.05 mg.

BRIEF DESCRIPTION OF THE DRAWINGS

- The invention is further described with reference to the drawings in which
- 20 Fig. 1 is a graph showing the in vitro dissolution rate of drospirenone from tablet cores, V1-V7 being batches containing micronized drospirenone, and V8 being a batch containing macrocrystalline drospirenone;
- 25 Fig. 2 is a graph showing the in vitro dissolution rate of drospirenone from tablet cores, different lines representing different test batches;
- Fig. 3 is a graph showing the in vitro dissolution rate of drospirenone from film-coated tablets, different lines representing different test batches;
- 30 Fig. 4 is a graph showing the in vitro dissolution rate of ethinylestradiol from tablet cores, different lines representing different test batches; and
- Fig. 5 is a graph showing the in vitro dissolution rate of ethinylestradiol from film-coated
- 35 tablets, different lines representing different test batches.

DETAILED DISCLOSURE OF THE INVENTION

Drospirenone, which may be prepared substantially as described in, e.g., US 4,129,564 or
5 WO 98/06738, is a sparingly soluble substance in water and aqueous buffers at various
pH values. Furthermore, drospirenone is rearranged to an inactive isomer under acid
conditions and hydrolysed under alkaline conditions. To ensure good bioavailability of the
compound, it is therefore advantageously provided in a form that promotes rapid
dissolution thereof.

10

It has surprisingly been found that when drospirenone is provided in micronized form (so
that particles of the active substance have a surface area of more than 10,000 cm²/g, and
the following particle size distribution as determined under the microscope: not more than
2 particles in a given batch with a diameter of more than 30 µm, and preferably ≤ 20

15 particles with a diameter of ≥ 10 µm and ≤ 30 µm) in a pharmaceutical composition, rapid
dissolution of the active compound from the composition occurs in vitro ("rapid
dissolution" is defined as the dissolution of at least 70% over about 30 minutes, in
particular at least 80% over about 20 minutes, of drospirenone from a tablet preparation
containing 3 mg of drospirenone in 900 ml of water at 37°C determined by the USP XXIII
20 Paddle Method using a USP dissolution test apparatus 2 at 50 rpm). Instead of providing
the drospirenone in micronized form, it is possible to dissolve it in a suitable solvent, e.g.
methanol or ethyl acetate, and spray it onto the surface of inert carrier particles followed
by incorporation of the particles containing drospirenone on their surface in the
composition.

25

Without wishing to be limited to any particular theory, it appears that the in vitro
dissolution rate of drospirenone is connected to the dissolution rate in vivo resulting in
rapid absorption of drospirenone in vivo on oral administration of the compound. This is
an advantage because isomerization of the compound in the gastric environment and/or
30 hydrolysis in the intestine is substantially reduced, leading to a high bioavailability of the
compound.

With respect to ethinylestradiol which is also a sparingly soluble substance, though less
sensitive to degradation than drospirenone under conditions prevailing in the

35 gastrointestinal tract, it is also an advantage to provide it in micronized form or sprayed

from a solution, e.g. in ethanol, onto the surface of inert carrier particles. This has the added advantage of facilitating a more homogenous distribution of the ethinylestradiol throughout the composition which might otherwise be difficult to obtain because ethinylestradiol is incorporated in extremely small amounts. When ethinylestradiol is provided in micronized form, it preferably has the following particle size distribution as determined under the microscope: 100% of the particles have a diameter of $\leq 15.0 \mu\text{m}$, 99% of the particles have a diameter of $\leq 12.5 \mu\text{m}$, 95% of the particles have a diameter of $\leq 10.0 \mu\text{m}$, and 50% of the particles have a diameter of $\leq 3.0 \mu\text{m}$. Furthermore, no particle is larger than $20 \mu\text{m}$, and ≤ 10 particles have a diameter of $\geq 15 \mu\text{m}$ and $\leq 20 \mu\text{m}$.

10

To obtain a more rapid rate of dissolution, it is preferred to include carriers or excipients which act to promote dissolution of both active substances. Examples of such carriers and excipients include substances that are readily soluble in water such as cellulose derivatives, carboxymethylcellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, gelled starch, gelatin or polyvinylpyrrolidone. In particular, it appears as though polyvinylpyrrolidone might be particularly helpful to promote dissolution.

15

The composition of the invention preferably comprises drospirenone in an amount corresponding to a daily dosage of from about 2.5 mg to about 3.5 mg, in particular about 3 mg. The amount of ethinylestradiol preferably corresponds to a daily dosage of from about 0.015 mg to about 0.04 mg, in particular from about 0.015 mg to about 0.03 mg. More particularly, the present composition comprises an amount of drospirenone corresponding to a daily dosage of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg.

20

Apart from its ability to inhibit ovulation, the composition of the invention has been found to possess pronounced anti-androgenic properties and may therefore be used in the prevention or treatment of androgen-induced disorders, in particular acne. Such use may be independent from or concomitant with the use as a contraceptive disclosed above. Furthermore, since drospirenone is an aldosterone antagonist, it has diuretic properties and is therefore suitable for counteracting the water-retentive properties of ethinylestradiol.

30

In a particular embodiment, the invention relates to a pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage

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units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein each of said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg.

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In one embodiment, the preparation further comprises 7 or less said daily dosage units containing no active agent. Alternatively, it is possible to include, in the dosage regimen, a period of 7 days or less during which no dosage units are ingested. For compliance reasons, however, it may be preferred to include an appropriate number of blanks in the preparation, in which case the total number of daily dosage units in the preparation is at least 28. The inclusion of blanks, or the pill-free days, will then trigger withdrawal bleeding.

The preparation may be a one-phase composition, i.e. a preparation wherein the amounts of either active agent remains constant for the entire at least 21-day period, or the amounts of either or both active agents may be varied over the at least 21-day period to generate a multiple-phase preparation, e.g. a two- or three-phase preparation, substantially as disclosed in, e.g., EP 148 724. In case of multiple-phase preparation, it may be possible to include a natural estrogen such as estradiol, e.g. in an amount of from about 0.5 mg to about 4 mg per day, instead of ethinylestradiol.

In suitable embodiments of the present preparation, the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol may be 21, 22, 23 or 24, and the number of daily dosage units containing no active agent may then be 7, 6, 5 or 4, as the case may be. In a further embodiment of the present preparation, the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 28, or a multiple of 28 such as 2-4, in particular 2 or 3, times 28.

In an alternative embodiment, the invention relates to a contraceptive preparation consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 consecutive days, wherein at least 21 of said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, and wherein 7 or less of

said daily dosage units contain ethinylestradiol alone in an amount from about 0.01 to about 0.05 mg.

By including an appropriate number of dosage units comprising ethinylestradiol alone,
5 high contraceptive reliability, low follicular development and satisfactory cycle control with little or no intermenstrual bleeding may be obtained.

In this case, too, the preparation may be one in which the amounts of either active agent remains constant for the entire at least 21-day period (i.e. a two-phase preparation), or the
10 amounts of either or both active agents may be varied over the at least 21-day period to generate a multiple-phase preparation, e.g. a three- or four-phase preparation, substantially as disclosed in, e.g., EP 148 724. In case of multiple-phase preparation, it may be possible to include a natural estrogen such as estradiol, e.g. in an amount of from about 0.5 mg to about 4 mg per day, instead of ethinylestradiol.

15

In suitable embodiments of the present preparation, the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol may be 21, 22, 23 or 24, and the number of daily dosage units containing ethinylestradiol alone may then be 7, 6, 5 or 4, as the case may be.

20

In one embodiment of the present method of inhibiting ovulation, the method comprises administering, to said mammal, on each day of at least 21 consecutive days, a daily dosage unit comprising a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, followed
25 by administering, on each day of 7 or less consecutive days, a daily dosage unit containing no active agent, or alternatively, administering no dosage units for 7 days or less.

In suitable embodiments of this method, the daily dosage units comprising the
30 combination of drospirenone and ethinylestradiol may be administered for 21, 22, 23 or 24 consecutive days, and the daily dosage units containing no active agent may then be administered for 7, 6, 5 or 4 consecutive days, as appropriate. Furthermore, the daily dosage units comprising the combination of drospirenone and ethinylestradiol may be administered for 28 consecutive days. In a variant of this embodiment, the daily dosage
35 units comprising the combination of drospirenone and ethinylestradiol are administered for

2-4, preferably 2 or 3, times 28 consecutive days, followed by administration of the daily dosage units comprising the combination of drospirenone and ethinylestradiol for 21, 22, 23 or 24 consecutive days and subsequently administration of the daily dosage units containing no active agent, or administration of no daily dosage units, for 7, 6, 5 or 4
5 consecutive days.

Alternatively, the present method comprises administering, on each day of at least 21 consecutive days, a daily dosage unit comprising a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about
10 0.01 to about 0.05 mg, followed by administering, on each day of 7 or less consecutive days, a daily dosage unit containing ethinylestradiol alone in an amount of from about 0.01 mg to about 0.05 mg.

In this alternative method, the daily dosage units comprising the combination of
15 drospirenone and ethinylestradiol may suitably be administered for 21, 22, 23 or 24 consecutive days, and wherein the daily dosage units comprising ethinylestradiol alone may then be administered for 7, 6, 5 or 4 consecutive days, as appropriate. In a further embodiment of the method, the daily dosage units comprising the combination of drospirenone and ethinylestradiol are administered for 2-4, preferably 2 or 3, times 28
20 consecutive days, followed by administration of the daily dosage units comprising the combination of drospirenone and ethinylestradiol for 21 consecutive days and subsequently administration of the daily dosage units comprising ethinylestradiol alone for 7 consecutive days.

25 For use according to the invention, the pharmaceutical preparation may suitably be in the form of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein each of said daily dosage units each comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an
30 amount from about 0.01 to about 0.05 mg.

As indicated above, the preparation may further comprise 7 or less daily dosage units containing no active agent (or may contain 7 or less empty "places", e.g. in the form of empty blisters in a blister pack, marking the days on which no daily dosage units are
35 administered).

Alternatively, the pharmaceutical preparation may be in the form of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 consecutive days, wherein at least 21 of said daily dosage units each comprises a combination of

- 5 drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount of from about 0.01 to about 0.05 mg, said packaging unit further comprising 7 or less daily dosage units comprising ethinylestradiol alone in an amount of from about 0.01 mg to about 0.05 mg.
- 10 The composition of the invention may be formulated in any manner known in the pharmaceutical art. In particular, as indicated above, the composition may be formulated by a method comprising providing drospirenone and, if desired, ethinylestradiol in micronized form in said unit dosage form, or sprayed from a solution onto particles of an inert carrier in admixture with one or more pharmaceutically acceptable excipients that
- 15 promote dissolution of the drospirenone and ethinylestradiol so as to promote rapid dissolution of drospirenone and preferably ethinylestradiol on oral administration. Examples of suitable excipients include fillers, e.g. sugars such as lactose, glucose or sucrose, sugar alcohols such as mannitol, sorbitol or xylitol, starch such as wheat, corn or potato starch, modified starch or sodium starch glycolate, lubricants such as talc,
- 20 magnesium stearate, calcium stearate, colloidal silica or stearic acid, and binders such as polyvinylpyrrolidone, cellulose derivatives, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose or gelatin, for making oral dosage forms such as tablets, pills or capsules.
- 25 Tablets may conveniently be coated with a suitable film-forming agent, e.g. hydroxypropylmethyl cellulose, hydroxypropyl cellulose or ethyl cellulose, to which a suitable excipient may optionally be added, e.g. a softener such as glycerol, propylene glycol, diethylphthalate or glycerol triacetate, filler such as sucrose, sorbitol, xylitol, glucose or lactose, a colorant such as titanium hydroxide, etc.
- 30 The present composition may also be formulated in liquid form, e.g. as a solution, suspension or emulsion, together with conventional diluents or excipients in a manner known per se in the pharmaceutical art.

A packaging unit comprising the daily dosage units described above may be prepared in a manner analogous to that of making other oral contraceptives. This may for instance be a conventional blister pack or any other form known for this purpose, for instance a pack comprising the appropriate number of dosage units (in this case at least 21, or for
5 particular applications, 28 or a multiple of 28) in a sealed blister pack with a cardboard, paperboard, foil or plastic backing and enclosed in a suitable cover. Each blister container may conveniently be numbered or otherwise marked, e.g. starting with the first of the at least 21 dosage units that contain the combination of drospirenone and ethinylestradiol, optionally followed by 7 or less empty blisters or by the 7 or less dosage units that contain
10 no active agent or that only contain ethinylestradiol (although the numbering may also start with the first of the 7 or less dosage units that only contain ethinylestradiol).

It is also envisaged that the present composition may be in the form of a parenteral formulation such as a subcutaneous implant or transdermal formulation. For making
15 implants, the active agents may suitably be formulated together with one or more polymers that are gradually eroded or degraded when in use, e.g. silicone polymers; ethylene vinylacetate, polyethylene or polypropylene.

Where transdermal formulations are concerned, they may be prepared in the form of
20 matrices or membranes or as fluid or viscous formulations in oil or hydrogels. For transdermal patches, an adhesive which is compatible with the skin should be included, such as polyacrylate, a silicone adhesive or polyisobutylene, as well as a foil made of, e.g. polyethylene, polypropylene, ethylene vinylacetate, polyvinylchloride, polyvinylidene chloride or polyester, and a removable protective foil made from, e.g., polyester or paper
25 coated with silicone or a fluoropolymer. For the preparation of transdermal solutions or gels, water or organic solvents or mixtures thereof may be used. Transdermal gels may furthermore contain one or more suitable gelling agents or thickeners such as silicone, tragacanth, starch or starch derivatives, cellulose or cellulose derivatives or polacrylic acids or derivatives thereof. Transdermal formulations may also suitably contain one or
30 more substances that enhance absorption through the skin, such as bile salts or derivatives thereof and/or phospholipids. Suitable transdermal formulations may, for instance, be made in a manner analogous to that described in WO 94/04157 for 3-ketodesogestrel. Alternatively, transdermal formulations may be prepared according to a method disclosed in, e.g., BW Barry, "Dermatological Formulations, Percutaneous

Absorption", Marcel Dekker Inc., New York - Basel, 1983, or YW Chien, "Transdermal Controlled Systemic Medications", Marcel Dekker Inc., New York - Basel, 1987.

The present invention is further described in the following examples which are not in any way intended to limit the scope of the invention as claimed.

EXPERIMENTAL

Example 1

10

Preparation of tablets containing drospirenone and ethinylestradiol

Tablet cores of the following composition

15	micronized drospirenone	3.00 mg
	micronized ethinylestradiol	0.03 mg
	lactose monohydrate	48.17 mg
	corn starch	14.40 mg
	modified starch	9.60 mg
20	polyvinylpyrrolidone 25,000	4.00 mg
	magnesium stearate	0.80 mg

were prepared by charging a fluidized bed granulator with 31.68 kg corn starch, 21.12 kg modified starch, 6.60 micronized drospirenone, 0.066 kg micronized ethinylestradiol and 25 105.974 kg lactose monohydrate and activating the fluidized bed. An aqueous solution of 8.80 kg polyvinylpyrrolidone 25,000 in 46.20 kg purified water was sprayed continuously onto the fluidized bed while drying by heating the air stream of the fluidized bed. At the end of the process 1.76 kg magnesium stearate was sucked into the granulator and mixed with the granules by maintaining the fluidized bed. The resulting granulate was pressed 30 into tablet cores by compression using a rotary tablet press.

2.22464 kg of hydroxypropylmethylcellulose and 0.44528 macrogol 6000 were dissolved in 14.67 kg purified water. 0.44528 kg talc, 1.22430 kg titanium dioxide and 0.06050 kg ferric oxide pigment were suspended in 10.26 kg purified water with stirring and

homogenized. The solution and suspension were combined and used to coat the tablet cores by continuous application of the coating suspension in a coater.

Example 2

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Dissolution of drospirenone from tablets

The rate of dissolution of drospirenone from the tablets prepared in Example 1 was determined by the USP XXIII Paddle Method using a USP Dissolution Test Apparatus 2 including 6 covered glass vessels and 6 paddles. Tablets were placed in 900 ml water at a temperature of 37°C ($\pm 0.5^\circ\text{C}$) and stirred at 50 rpm.

The results appear from Figs. 1, 2 and 4. From Fig. 1, it appears that the batch numbered V8 containing macrocrystalline drospirenone (but otherwise identical to the tablets prepared in Example 1) exhibited an extremely slow dissolution rate of drospirenone, whereas all batches containing micronized drospirenone exhibited a dissolution rate of more than 70% within 30 minutes.

Fig. 2 and Fig. 4 shows the results of dissolution of drospirenone from tablet cores and film-coated tablets, respectively. In both cases more than 70% of the active agent is dissolved within 30 minutes. Thus, the film coating did not significantly influence the rate of dissolution.

Example 3

25 *Dissolution rate of ethinylestradiol from tablets in vitro*

The rate of dissolution of ethinylestradiol from tablets prepared as described in Example 1 was determined according to the USP Paddle Method as described in Example 2 for drospirenone. The results appear from Figs. 3 and 5 showing the dissolution rates from tablet cores and film-coated tablets, respectively. In both cases, more than 70% of the active agent was dissolved within 30 minutes. Thus, the film coating did not significantly influence the rate of dissolution.

Example 4

Bioavailability of drospirenone and ethinylestradiol from tablets containing 3 mg of drospirenone and 0.03 mg ethinylestradiol

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42 healthy women between 18 and 35 years of age were included in an open-label crossover study after their informed consent had been obtained. The aim of the study was to investigate the relative bioavailability of drospirenone and ethinylestradiol from a tablet formulation containing 3 mg drospirenone and 0.03 mg ethinylestradiol with reference to
10 an oral suspension containing 6 mg of drospirenone and 0.06 mg ethinylestradiol per vial.

The bioavailability was determined using serum concentrations of each active agent as parameters. Compared to the oral suspension, the relative bioavailability of drospirenone and ethinylestradiol from the tablets is 107% and 117%, respectively. It was therefore
15 concluded that both drospirenone and ethinylestradiol are completely released from the tablets in vivo.

The absolute bioavailability of drospirenone was determined in two studies to be 76%±13% after oral administration of 2 mg drospirenone to 8 young healthy women and
20 85%±24% after oral administration of a microcrystalline suspension containing 3.13 mg drospirenone to 6 postmenopausal women.

The oral bioavailability of ethinylestradiol was determined in several studies, and mean values of from 36% to 59% were reported in the literature, indicating a first-pass effect.

25

Example 5

Contraceptive efficacy of formulations containing drospirenone and ethinylestradiol

30 An open-label, randomized trial with 52 female volunteers aged 20-35 years whose informed consent had been obtained included 1 pre-treatment cycle, 3 treatment cycles with two different tablet containing 2 mg and 3 mg drospirenone, respectively, but otherwise corresponding to the tablets prepared in Example 1, and a follow-up phase. A wash-out phase of 1 month preceded the treatment.

35

At defined time points, selected central and peripheral parameters were investigated: LH, FSH, 17β -estradiol, progesterone, cervical score, "spinnbarkeit", fern phenomenon.

Ovarian function was checked by ultrasound. In addition, SHBG, CBG, prolactine, total testosterone, androstenedione, DHEA-S and selected metabolic parameters (serum

5 glucose, triglycerides, cholesterol, HDL, LDL) were examined. Blood pressure, heart rate, body weight and cycle control were documented.

The results of the study showed that both LH and FSH were clearly suppressed with both trial preparations. Accordingly, the secretion of estradiol and progesterone were greatly

10 reduced over all three treatment cycles with the exception of 3 volunteers receiving the 2 mg drospirenone preparation. This result was, in principle, confirmed by the

accompanying ultrasound examinations. Follicular ripening occurred in several cases with

both trial preparations. Although three ovulations were diagnosed with the preparation

containing 2 mg drospirenone (one of which was described as "equivocal" and the other

15 as a "tablet-taking error"), no differences were demonstrable statistically ($p > 0.05$)

between the two trial preparations as regards the hormones LH, FSH, estradiol and

progesterone, and the parameter "ovulation during the treatment cycles". In keeping with

the hormones, cervical function was greatly limited and the "spinnbarkeit" and

crystallisability of the cervical mucus was greatly reduced with both trial preparations.

20 Prolactin increased minimally and SHBG and CBG distinctly with both preparations.

Triglycerides and HDL levels increased with both trial preparations, while LDL levels

decreased. Total cholesterol was largely unchanged in both treatment groups. Oral

glucose tolerance remained virtually unchanged or was slightly decreased. Testosterone, androstenedione and DHEA-S decreased minimally.

25

The subjective and objective tolerance was good with both treatments. This was also the

case for cycle control with the exception of the first cycle with 2 mg drospirenone. Blood

pressure, heart rate and body weight remained constant in the majority of cases or

showed a slight tendency to decrease.

30

After three months' treatment, it was concluded:

The two trial preparations were equally good as regards the subjective and objective tolerance.

No negative metabolic effects were observed with either preparation. HDL was influenced positively in the sense of an increase.

The results confirmed the results of earlier studies that the 2 mg drospirenone preparation was in the threshold region of ovulation inhibition, whereas the 3 mg drospirenone
5 preparation had a demonstrable ovulation-inhibiting effect in all cases examined.

CLAIMS

1. A pharmaceutical composition comprising, as a first active agent, 6 β ,7 β ;15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (drospirenone) in an amount
5 corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and, as a second active agent, 17 α -ethinylestradiol (ethinylestradiol) in an amount corresponding to a daily dosage of from about 0.01 mg to about 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients.
- 10 2. A composition according to claim 1 wherein the drospirenone is in micronized form or sprayed from a solution onto particles of an inert carrier.
3. A composition according to claim 1 or 2, comprising drospirenone in an amount corresponding to a daily dosage of from about 2.5 mg to about 3.5 mg, in particular about
15 3 mg.
4. A composition according to claim 1 wherein the ethinylestradiol is in micronized form or sprayed from a solution onto particles of an inert carrier.
- 20 5. A composition according to claim 1 or 4, comprising ethinylestradiol in an amount corresponding to a daily dosage of from about 0.015 mg to about 0.04 mg, in particular from about 0.02 mg to about 0.03 mg.
6. A composition according to any of the preceding claims, comprising an amount of
25 drospirenone corresponding to a daily dosage of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg, in particular comprising an amount of drospirenone corresponding to a daily dosage of about 3.0 mg and ethinylestradiol in an amount corresponding to a daily dosage of 0.03 mg.
- 30 7. A composition according to any of the preceding claims wherein the pharmaceutically acceptable carrier or excipient is selected so as to promote rapid dissolution of the first and second active agents.
8. A composition according to any of the preceding claims wherein at least 70% of the first
35 and second active substance are released within 30 minutes of administration thereof.

9. A composition according to claim 8, wherein at least 80% of the first and second active agents are released within 20 minutes of administration thereof.

5 10. A pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg.

10

11. A preparation according to claim 10, which additionally comprises 7 or less daily dosage units containing no active agent intended for oral administration subsequent to the period of at least 21 consecutive days, the total number of daily dosage units being at least 28.

15

12. A preparation according to claim 10 or 11, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 21, 22, 23 or 24, and wherein the number of daily dosage units containing no active agent is 7, 6, 5 or 4.

20

13. A preparation according to claim 10, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 28, or a multiple of 28 such as 2-4, in particular 2 or 3, times 28.

25

14. A preparation according to claim 13, which additionally comprises a number of daily dosage units comprising the combination of drospirenone and ethinylestradiol of 21, 22, 23 or 24, and a number of daily dosage units containing no active agent of 7, 6, 5 or 4.

30

15. A preparation according to any of claims 10-14, wherein the at least 21 daily dosage units comprise drospirenone and ethinylestradiol in micronized form or sprayed from a solution onto particles of an inert carrier.

35

16. A preparation according to any of claims 10-15 wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 2.5 mg to about 3.5 mg, in particular about 3 mg, and ethinylestradiol in an amount of from about 0.015 mg to about 0.04 mg, in particular from about 0.015 mg to about 0.03 mg.

17. A preparation according to any of claims 10-16, wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg.

5

18. A pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 consecutive days, wherein at least 21 of said daily dosage units comprises a combination of drospirenone in an amount of from about 2
10 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, and wherein 7 or less of said daily dosage units contain ethinylestradiol alone in an amount from about 0.01 to about 0.05 mg.

19. A preparation according to claim 18, wherein the number of daily dosage units
15 comprising the combination of drospirenone and ethinylestradiol is 21, 22, 23 or 24, and wherein the number of daily dosage units comprising ethinylestradiol alone is 7, 6, 5 or 4.

20. A preparation according to claim 18 or 19, wherein the at least 21 daily dosage units comprise drospirenone and ethinylestradiol in micronized form or sprayed from a solution
20 onto particles of an inert carrier.

21. A preparation according to any of claims 18-20, wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 2.5 mg to about 3.5 mg, in particular about 3 mg, and ethinylestradiol in an amount of from about 0.015 mg to about
25 0.04 mg, in particular from about 0.02 mg to about 0.03 mg.

22. A preparation according to any of claims 18-21, wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg.

30

23. A method of inhibiting ovulation in a mammal, in particular a human, comprising administering, to said mammal, drospirenone in an amount in the range of from about 2 mg to about 4 mg of per day, together with ethinylestradiol in an amount of from about 0.01 mg to about 0.05 mg per day, said amounts being effective to inhibit ovulation in said
35 mammal.

24. A method according to claim 23, wherein the amount of drospirenone is in the range of from about 2.5 mg to about 3.5 mg, in particular about 3 mg of drospirenone per day.

5 25. A method according to claim 23, wherein the amount of ethinylestradiol is from about 0.015 mg to about 0.04 mg, in particular from about 0.015 to about 0.03 mg per day.

26. A method of preventing or treating androgen-induced disorders in a female mammal, in particular a female human, comprising administering, to said mammal, an amount of
10 drospirenone in the range of from about 2 mg to about 4 mg per day, together with an amount of ethinylestradiol of from about 0.01 mg to about 0.05 mg per day, said amounts being effective to prevent or treat androgen-induced disorders in said mammal.

27. A method according to claim 26, wherein the androgen-induced disorder is acne.
15

28. A method of inhibiting ovulation in a mammal, in particular a human, comprising administering, to said mammal, on each day of at least 21 consecutive days, a daily dosage unit comprising a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, followed
20 by administering, on each day of 7 or less consecutive days, a daily dosage unit containing no active agent, or alternatively administering no daily dosage units for 7 or less consecutive days.

29. A method according to claim 28, wherein the daily dosage units comprising the
25 combination of drospirenone and ethinylestradiol are administered for 21, 22, 23 or 24 consecutive days, and wherein no daily dosage units or daily dosage units containing no active agent are administered for 7, 6, 5 or 4 consecutive days.

30. A method according to claim 28, wherein the daily dosage units comprising the
30 combination of drospirenone and ethinylestradiol are administered for 28 consecutive days.

31. A method according to claim 28, wherein the daily dosage units comprising the combination of drospirenone and ethinylestradiol are administered for 2-4, preferably 2 or
35 3, times 28 consecutive days, followed by administration of the daily dosage units

comprising the combination of drospirenone and ethinylestradiol for 21 consecutive days and subsequently administration of the daily dosage units containing no active agent, or alternatively no daily dosage units, for 7 consecutive days.

- 5 32. A method of inhibiting ovulation in a mammal, in particular a human, comprising administering, to said mammal, on each day of at least 21 consecutive days, a daily dosage unit comprising a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, followed by administering, on each day of 7 or less consecutive days, a daily dosage unit
10 containing ethinylestradiol alone in an amount of from about 0.01 mg to about 0.05 mg.

33. A method according to claim 32, wherein the daily dosage units comprising the combination of drospirenone and ethinylestradiol are administered for 21, 22, 23 or 24 consecutive days, and wherein the daily dosage units comprising ethinylestradiol alone
15 are administered for 7, 6, 5 or 4 consecutive days.

34. A method according to claim 32, wherein the daily dosage units comprising the combination of drospirenone and ethinylestradiol are administered for 2-4, preferably 2 or 3, times 28 consecutive days, followed by administration of the daily dosage units
20 comprising the combination of drospirenone and ethinylestradiol for 21 consecutive days and subsequently administration of the daily dosage units comprising ethinylestradiol alone for 7 consecutive days.

35. A method of promoting rapid dissolution of drospirenone from a unit dosage form on
25 oral administration, the method comprising providing drospirenone in micronized form in said unit dosage form, or sprayed from a solution onto particles of an inert carrier in admixture with one or more pharmaceutically acceptable excipients that promote dissolution of the drospirenone.

- 30 36. Use of drospirenone combined with ethinylestradiol for preparing a pharmaceutical preparation for the inhibition of ovulation in a mammal, in particular a human, the composition comprising an amount of drospirenone corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and comprising an amount of ethinylestradiol corresponding to a daily dosage, on administration of the
35 composition, of from about 0.01 to about 0.05 mg.

37. Use according to claim 36, wherein the drospirenone is in micronized form, or sprayed from a solution onto particles of an inert carrier.

5 38. Use according to claim 36, wherein the amount of drospirenone corresponds to a daily dosage of from about 2.5 mg to about 3.5 mg, in particular about 3.0 mg.

39. Use according to claim 36, wherein the amount of ethinylestradiol corresponds to a daily dosage of from about 0.015 mg to about 0.04 mg, in particular from about 0.02 mg to
10 about 0.03 mg.

40. Use according to claim 36, wherein the ethinylestradiol is in micronized form, or sprayed from a solution onto particles of an inert carrier.

15 41. Use according to claim 36 for the prevention or treatment of androgen-induced disorders in a female mammal, in particular a female human.

42. Use according to claim 41, wherein the androgen-induced disorder is acne.

20 43. Use of a combination of drospirenone and ethinylestradiol for preparing a pharmaceutical preparation for the inhibition of ovulation in a mammal, in particular a human, the preparation being in the form of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein said daily dosage
25 units each comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg.

44. Use according to claim 43, wherein the preparation further comprises 7 or less daily dosage units containing no active agent, the total number of daily dosage units being at
30 least 28.

45. Use of a combination of drospirenone and ethinylestradiol for preparing a pharmaceutical preparation for the inhibition of ovulation in a mammal, in particular a human, the preparation being in the form of a number of separately packaged and
35 individually removable daily dosage units placed in a packaging unit and intended for oral

administration for a period of at least 28 consecutive days, wherein at least 21 of said daily dosage units each comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount of from about 0.01 to about 0.05 mg, said packaging unit further comprising 7 or less daily dosage units comprising

5 ethinylestradiol alone in an amount of from about 0.01 mg to about 0.05 mg.

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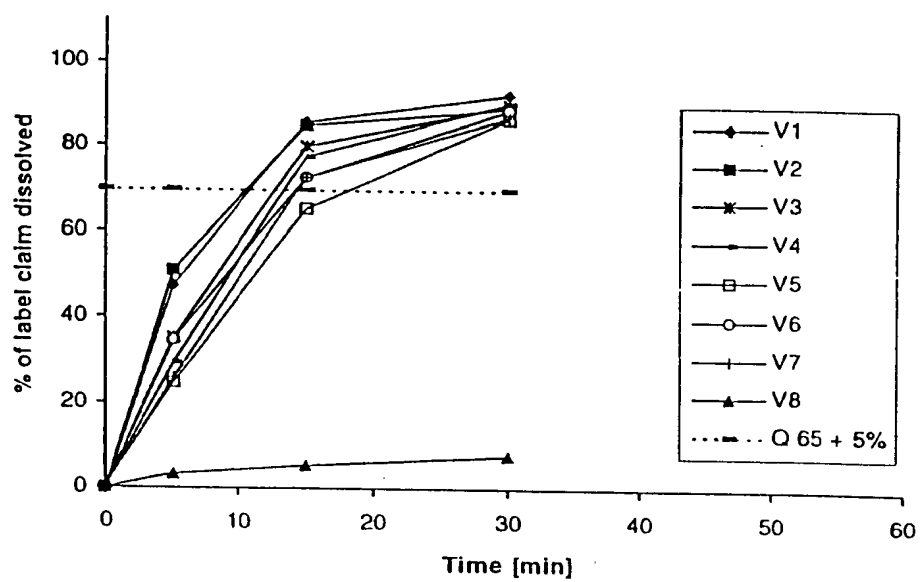


Fig. 1

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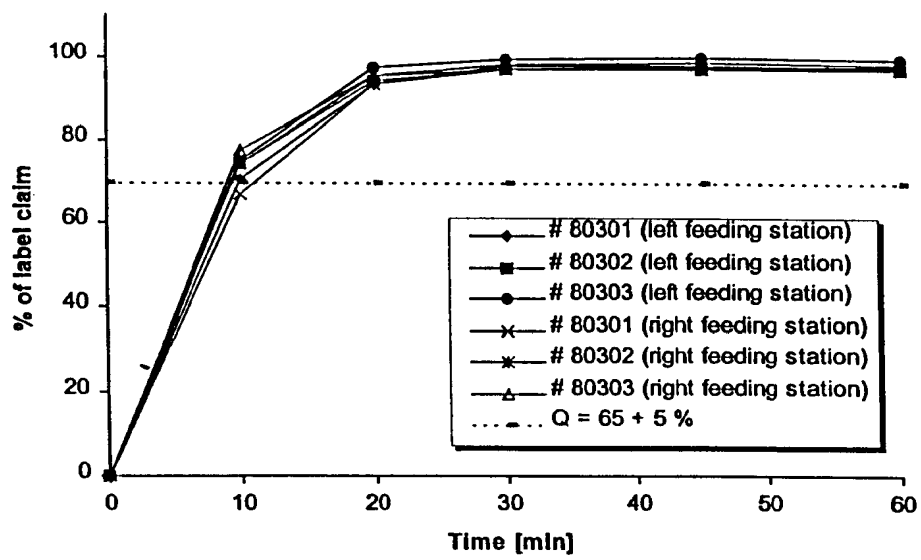


Fig. 2

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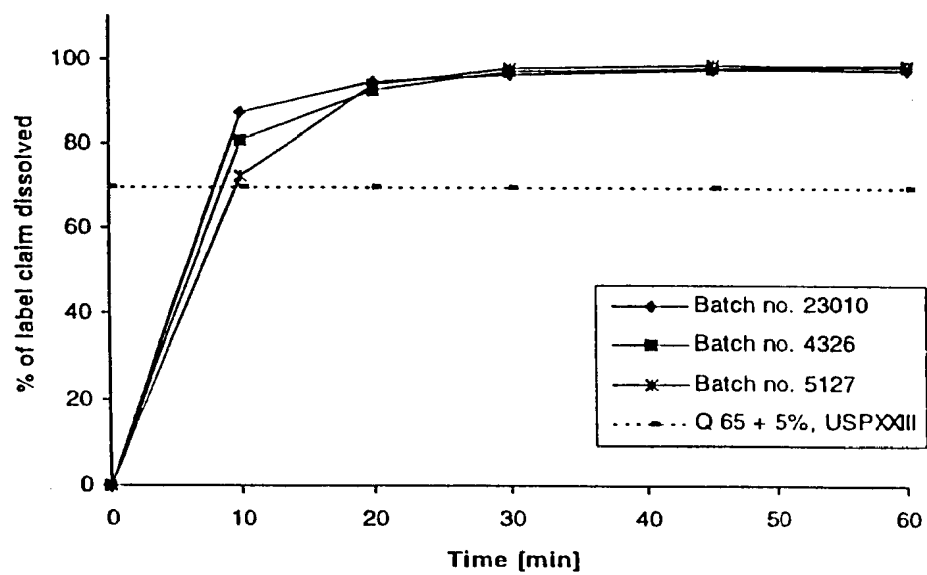


Fig. 3

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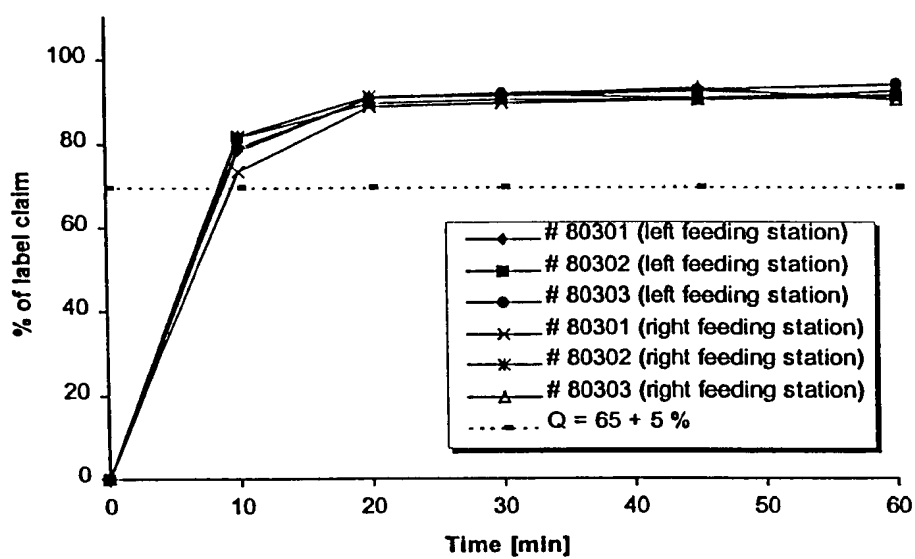


Fig. 4

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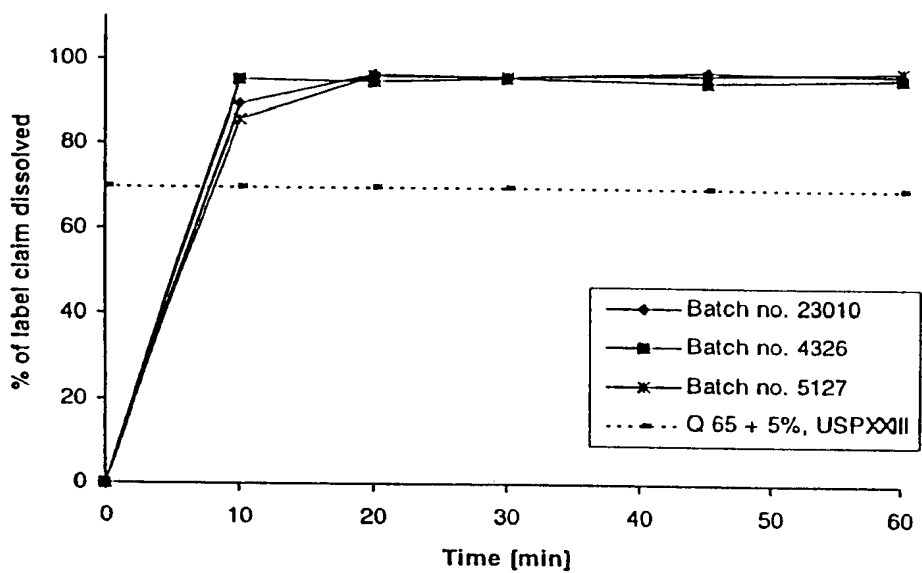


Fig. 5

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 00/01213

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/565 A61K31/585 A61P15/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 26730 A (SCHERING AG ; LACHNIT URSULA (DE); DUESTERBERG BERND (DE); SPONA JU) 12 October 1995 (1995-10-12) abstract; claims 1-4; example 1 ---	1, 3, 5, 6, 10-14, 16-19, 21-26, 28-34, 36, 38, 41, 43-45
X	WO 98 04267 A (AMERICAN HOME PROD) 5 February 1998 (1998-02-05) abstract --- <div style="text-align: center;">-/-</div>	1, 3, 5, 6, 10-14, 16-19, 21-26, 28-34, 36, 38, 41, 43-45
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents:</p> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*Z* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center;">16 January 2001</div>		Date of mailing of the international search report <div style="text-align: center;">23/01/2001</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016		Authorized officer <div style="text-align: center;">Gonzalez Ramon, N</div>

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 00/01213

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 95 17194 A (SCHERING AG) 29 June 1995 (1995-06-29)</p> <p>abstract; claims 1,2,7,13 ---</p>	<p>1,3,5,6, 10-14, 16-19, 21-26, 28-34, 36,38, 41,43-45</p>
X	<p>WO 98 04269 A (AMERICAN HOME PROD) 5 February 1998 (1998-02-05)</p> <p>abstract page 9, line 20-25; claims 3,5,18-21,23,29 ---</p>	<p>1,3,5,6, 10-14, 16-19, 21-26, 28-34, 36,38, 41,43-45</p>
X	<p>WO 97 01342 A (SCHERING AG ;SCHMIDT GOLLWITZER KARIN (DE); KLEMMANN WALTER (DE)) 16 January 1997 (1997-01-16)</p> <p>abstract; claims 6-9,18,19,27-29,37-39; examples 1-3 ---</p>	<p>1,3,5,6, 10-14, 16-19, 21-26, 28-34, 36,38, 41,43-45</p>
X	<p>OELKERS W K H: "Effects of estrogens and progestogens on the renin-aldosterone system and blood pressure" STEROIDS: STRUCTURE, FUNCTION, AND REGULATION,US,ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, vol. 61, no. 4, 1 April 1996 (1996-04-01), pages 166-171, XP004026568 ISSN: 0039-128X abstract; table 1 ---</p>	<p>1,3,5,6, 10-14, 16-19, 21-26, 28-34, 36,38, 41,43-45</p>
X	<p>OELKERS W ET AL: "EFFECTS OF A NEW ORAL CONTRACEPTIVE CONTAINING AN ANTIMINERALOCORTICOID PROGESTOGEN, DROSPIRENONE, ON THE RENIN-ALDOSTERONE SYSTEM, BODY WEIGHT, BLOOD PRESSURE, GLUCOSE TOLERANCE, AND LIPID METABOLISM" JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM,US,NEW YORK, NY, vol. 80, no. 6, 1 June 1995 (1995-06-01), pages 1816-1821, XP002046619 ISSN: 0021-972X see methods abstract ---</p>	<p>1,3,5,6, 10-14, 16-19, 21-26, 28-34, 36,38, 41,43-45</p>

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 00/01213

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MUHN P ET AL.: "Drospirenone: a novel progestogen with antimineralocorticoid and antiandrogenic activity. Pharmacological characterization in animal models." CONTRACEPTION, (1995 FEB) 51 (2) 99-110., XP000908817	1,3,5,6, 10-14, 16-19, 21-26, 28-34, 36,38, 41,43-45
Y	abstract page 106	2,4,15, 20,35, 37,40
Y	----- NUERNBERG E.: "Manufacturing and properties of spray dried products!.. HERSTELLUNG UND EIGENSCHAFTEN PHARMAZEUTISCHER SPRUHTROCKNUNGSPRODUKTE." ACTA PHARMACEUTICA HUNGARICA, (1978) 48/1 (19-35). CODEN: APHGAO, XP000908820 abstract page 33 -----	2,4,15, 20,35, 37,40

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

Claims Nos.: 7-9

Present claims 7-9 relate to a carrier/excipient defined by reference to a desirable characteristic or property, namely "to promote rapid dissolution" without defining the chemical nature of said carrier/excipient. The claims cover all products/compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products/compounds specifically mentioned in the examples and the claims with due regard to the general idea underlying the present application

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 00/01213

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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